Antibiotic prophylaxis for infective endocarditis

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Infective endocarditis (IE) remains a major medical concern because of its mortality and costs, and because its incidence is not decreasing [1,2]. The prevention of this severe infection has long been considered desirable and possible; this has relied mainly on the administration of antibiotics to cardiac patients at risk before they undergo a procedure considered to carry risk. However, the indications for preventive treatment and the design of antibiotic regimens are not based on well-established scientific evidence, and recent studies have questioned the benefit of such treatment [3–6]. Recommendations for prophylaxis of IE have been established in most countries and regularly updated for more than 30 years, so they vary slightly from country to country [7–12]. It is not the objective of this report to change national guidelines, but (1) to analyze comparatively the guidelines from seven different countries, namely France, Germany, the Netherlands, Scandinavia, Switzerland, the UK and the USA, and (2) to identify the points of agreement which can be the basis for uniform international recommendations, and those aspects which are still subjects of debate.

Prophylactic antibiotics can be defined for certain conditions but (1) they cannot prevent every case of IE occurring in cardiac patients at risk or following procedures that carry risk, (2) they are distinct from antibiotic treatment of infectious episodes and foci of infection, which require rigorous treatment in cardiac patients at risk, (3) they do not apply to prevention of early postsurgical IE, for which different antibiotic regimens are required and which is excluded from this review, and, finally (4) antibiotic prophylaxis is only one aspect of the general prevention of IE.

The propositions presented below have been established through a group of international experts which was convened on 15 October 1992 to reach agreement on various topics concerning IE, among which was antibiotic prophylaxis. This group had two meetings and presented its conclusions for prophylaxis of IE at the Meeting of the International Society for Chemotherapy, in Stockholm, Sweden, July 1993. The following report is an attempt to summarize the discussions. It first presents an analytic description of the recommendations from various countries, and second, a synthetic analysis which comprise the propositions of the working group.

COMPARATIVE ANALYSIS OF NATIONAL RECOMMENDATIONS

Cardiac risk

According to the different countries, the cardiac conditions predisposing to endocarditis which require antibiotic prophylaxis are very similar. Some countries have distinguished between the cardiac diseases at risk and those which are not at risk. Some countries have identified a subgroup of cardiac diseases which are considered to carry high risk among the cardiac diseases at risk. This estimation of the relative risk of IE according to the cardiac condition is based on limited scientific data. Thus, from country to country, the antibiotic regimen recommended for a given procedure

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Table 1 Influence of the cardiac risk on the antibiotic schedules for prophylaxis of IE in different countries [7–12]

	Type of procedure		
	Dental (oral regimen)	Dental (parenteral regimen)	Gastrointestinal or urologic
France	No	No	No
Germany	Yes	–	Yes
The Netherlands	No	No	No
Switzerland	Yes	Yes	No
UK	No	Yes	No
US	No	Yes	No

No = same regimen in all cardiac patients at risk.
Yes = different regimen for cardiac patients at risk and cardiac patients at high risk.

may vary according to the supposed cardiac risk (Table 1).

Procedures at risk

The risk of IE associated with various procedures has not been assessed in prospective studies until recently. Most of the recommendations rely on anecdotal clinical reports and data from experimental models [13–17]. Most dental procedures are considered to confer risk; in some countries, prophylaxis is limited to procedures resulting in gingival or mucosal bleeding. Concerning non-dental procedures, several procedures in the oropharynx and upper respiratory tract are supposed to be covered with antibiotics. There are controversies concerning flexible bronchoscopy with or without biopsy, considered to be associated with risk in France and in Switzerland (for high-risk cardiac patients) and not in The Netherlands, the UK and the USA. Surgery on the digestive and urinary tracts is considered to be a risk in most countries. In some countries, coloscopy with biopsy is considered for prophylaxis only in high-risk patients. There is a similar debate concerning vaginal hysterectomy, vaginal delivery or fitting of an intrauterine device. There is also an extensive debate concerning transesophageal echocardiography.

Antibiotic schedules

Oral prophylaxis for dental and upper respiratory tract procedures (Table 2)

The regimen consists of amoxycillin 3 g given orally 1 h before the procedure in most countries. In some countries, oral penicillin is an alternative. A second or several additional doses of amoxycillin are recommended in some countries, especially for high-risk patients. In some countries this oral regimen is also used for some gastrointestinal procedures, in low-risk patients. For patients allergic to β-lactams, clindamycin is the most common recommendation, the dose varying from 300 to 600 mg. Alternative antibiotics, erythromycin or pristinamycin, are proposed in other countries.

Table 2 Comparison of the national recommendations for prophylaxis of IE: oral prophylaxis, dental care [7–12]

Patients not allergic to penicillin	
Common to all	*Amoxycillin 3 g 1 h before*
France	No second dose
Germany	Penicillin 2 million units[a]
The Netherlands	No second dose
Scandinavia	No second dose
Switzerland	+ 750 mg × 7 (if high risk)
UK	No second dose
USA	+ 1.5 g, 6 h later
Patients allergic to penicillin	
Common to all	*Clindamycin 1 h before*
France	600 mg or pristinamycin 1 g
Germany	600 mg
The Netherlands	Erythromycin[b] 1 g + 500 mg × 3
Scandinavia	300–600 mg
Switzerland	600 mg + 300 mg × 7 (if high risk)
UK	600 mg
USA	300 mg + 150 mg, 6 hours later or erythromycin 1 g stearate or 800 mg succinate + 500 mg (400 mg) 6 h later

[a] Instead of amoxycillin.
[b] Instead of clindamycin.

Parenteral prophylaxis for dental and upper respiratory tract procedures (Table 3)

The common regimen is based on ampicillin or amoxycillin given as an intravenous infusion 1 h before the procedure, completed with a second oral dose 6 h later. There are differences in the dosages of ampicillin used in the different countries. Aminoglycosides are not added in some countries, while they are recommended in others, especially in high-risk

Table 3 Comparison of the national recommendations for prophylaxis of IE: Parenteral prophylaxis; dental care [7–12]

Patients not allergic to penicillin	
Common to all	*Amoxycillin–Ampicillin* *IV infusion 1 h before* *+ one oral second dose 6 h later*
France	2 g + 1 g orally, 6 h later
Germany	Penicillin G 2M[a] + gentamicin 80 mg or streptomycin 0.5 g IM or IV
The Netherlands	Bicillin 1.2M[a]
Scandinavia	2 g + gentamicin 2–3 mg/kg
Switzerland	1 g + 1 g IV × 5 doses or 750 mg orally × 7 doses[b] + gentamicin 120 mg + 80 mg × 5 doses IM or IV[b]
UK	1 g + 0.5 g orally, 6 h later + gentamicin 120 mg IM or IV[b]
USA	2 g + 1 g orally, 6 h later + gentamicin 80 mg IM or IV[b]
Patients allergic to penicillin	
Common to all	*Vancomycin 1 g* *IV 1–2 h infusion*
France	Or teicoplanin 400 mg IV bolus
Germany	–
The Netherlands	Erythromycin 500 mg IV + 500 mg IV 6 h later
Scandinavia	–
Switzerland	+ 1 g × 3 doses[b] + gentamicin[b] 120 mg + 80 mg × 5 doses IM or IV
UK	+ gentamicin 120 mg IM or IV
USA	–

[a]Instead of amoxycillin.
[b]If high-risk patient.

patients. For allergic patients, vancomycin 1 g as an intravenous infusion is proposed. Teicoplanin, which can be given as a 400-mg intravenous bolus, or intravenous clindamycin are possible alternatives to vancomycin in some countries.

Gastrointestinal and urologic procedures (Table 4)

In general, parenteral prophylaxis is recommended. However, in some countries, low-risk patients may be given oral antibiotics. The antibiotic regimens are similar to those used for parenteral prophylaxis of dental procedures, except that an aminoglycoside is added in all countries in order to have maximal activity against enterococci, and clindamycin is not suitable because it is not sufficiently active against fecal streptococci.

SYNTHETIC ANALYSIS—PROPOSALS OF THE GROUP OF EXPERTS

Cardiac risk

The risk of bacterial seeding on cardiac valves remains difficult to assess, since rigorous epidemiologic data are limited. Only patients with a prosthetic valve constitute a well-defined population at risk [18–20]. In these patients, as in patients with previous endocarditis, the risk seems approximately 5–10 times higher than in patients with native valve disease. The other cardiac diseases at risk are listed in Table 5. The risk associated with pure mitral stenosis is mild to moderate. It is

Table 4 Comparison of the national recommendations for prophylaxis of IE: parenteral prophylaxis, gastrointestinal and urologic procedures [7–12]

Patients not allergic to penicillin	
Common to all	*Amoxycillin–Ampicillin* *IV infusion 1 h before* *+ one oral second dose 6 h later* + gentamicin IM or IV
France	Amoxycillin 2 g + 1g orally, 6 h later + gentamicin 1.5 mg/kg
Germany	Ampicillin 2 g[a] + gentamicin 80 mg
The Netherlands	Ampicillin 1 g + 1g orally, 6 h later + gentamicin 1.5 mg/kg + 1.5 mg/kg 6 h later
Scandinavia	Ampicillin 2 g + gentamicin 2–3 mg/kg[a]
Switzerland	Amoxycillin 1 g + 1g IV × 5 doses[b] or 750 mg orally × 7 doses[b] + gentamicin 120 mg + 80 mg × 5 doses[b]
UK	Amoxycillin 1 g + 0.5 g orally, 6 h later + gentamicin 120 mg
USA	Ampicillin 2 g + 1.5 g orally, 6 h later + gentamicin 80 mg
Patients allergic to penicillin	
Common to all	*Vancomycin 1 g* *IV 1–2 h infusion* *+ gentamicin IM or IV*
France	or teicoplanin 400-mg IV bolus + gentamicin 1.5 mg/kg
Germany	–
The Netherlands	Erythromycin 500 mg IV + 500 mg IV 6 h later + gentamicin 1.5 mg/kg + 1.5 mg/kg 6 h later
Scandinavia	+ gentamicin 2–3 mg/kg
Switzerland	+ 1g × 3 doses[b] + gentamicin 120 mg + 80 mg × 5 doses[b]
UK	or teicoplanin 400-mg IV bolus + gentamicin 120 mg
USA	+ 1 g IV infusion, 8 h later[b] + gentamicin 80 mg + 80 mg, 8 h later[b]

[a] No second dose.
[b] If high-risk patient.

Table 5 Cardiac conditions at risk requiring antibiotic prophylaxis for IE—International Consensus

Cardiac diseases with the highest risk
Prosthetic valves
Congenital heart disease causing cyanosis
Previous IE
Other cardiac diseases at risk
Valvular heart disease[a]: AR, MR, AS, including MVP with MR, and bicuspid aortic valve
Congenital heart disease which does not cause cyanosis, except IAC
Hypertrophic obstructive cardiomyopathy

AR, aortic regurgitation; MR, mitral regurgitation; AS, aortic stenosis; MVP, mitral valve prolapse; IAC, interatrial communication.
[a] The risk associated with pure mitral stenosis is debated.

Table 6 Cardiac diseases not at risk for IE—International Consensus

IAC
MVP without MR, functional MI, mitral ring calcifications
Coronary artery bypass grafting
Cardiac pacemakers
Implantable defibrillators
Corrected left-to-right shunts

IAC, interatrial communication; MVP, mitral valve prolapse; MR, mitral regurgitation; MI, mitral insufficiency.

Table 7 Procedures at risk for IE requiring antibiotic prophylaxis—International Consensus

Dental	All procedures
Upper respiratory tract	Tonsillectomy—adenoidectomy
Gastrointestinal	Esophageal dilatation or surgery Endoesophageal laser procedures Sclerosing procedures of esophageal varices Abdominal surgery
Urologic	Instrumental procedures involving the ureter or the kidney Biopsy or surgery of prostate or urinary tract
Procedures for which the risk of infective endocarditis is controversial	
Upper respiratory tract	Fiberoptic fibroscopy Endotracheal tube insertion
Gastrointestinal	Coloscopy with or without biopsy
Genital	Vaginal hysterectomy, vaginal delivery[a]

[a] However, antibiotic treatment is required in cases of concomitant infection.

suggested that a single antibiotic regimen be scheduled for all cardiac patients at risk, with a flexible formulation allowing the optimal regimen to be highly recommended for the patients with the highest risk. Furthermore, it appears worthwhile establishing the list of cardiac conditions which are not associated with risk of IE and do not require specific prophylaxis (Table 6).

Procedures at risk

It is widely accepted that dental procedures are the main risk factors for IE [6] and should all be covered with antibiotic prophylaxis, with the only exceptions being procedures without any risk of bleeding, such as superficial caries and bloodless supragingival prosthetic preparations. Application of a local antiseptic is recommended, as an adjunct to antibiotic prophylaxis. It must be recalled that regular dental care is mandatory in all patients at risk. Apart from the mouth, it is difficult to identify with any accuracy the procedures which carry a risk of infective endocarditis and to quantify this risk. The procedures considered to carry risk are those responsible for bacteremia with a consistent frequency: however, it does not necessarily predict the risk of IE [21]. The duration of the procedure is a possible factor which has to be considered. Some procedures are supposed to be covered in all countries (Table 7). It is especially important to underline that negative urine culture should be obtained before urologic procedures. Gyneco-obstetric procedures are not in general, considered to be at risk [22]. Fitting of an intrauterine device is not encouraged in cardiac women at risk, except in developing countries, where the risk of pregnancy should be weighed against the risk of IE. Also, patients undergoing transesophageal echocardiography should not be given antibiotic prophylaxis [23]. Although, for controversial procedures, no consensual recommendation can be made for routine use, in particular situations one practitioner may wish to give a patient some antibiotics.

Antibiotic prophylaxis should be directed against viridans streptococci of the oropharyngeal flora in procedures involving the oropharynx and upper respiratory tract, and against enterococci of the digestive flora for gastrointestinal and urologic procedures.

Antibiotic regimens

In general, antibiotics for dental and upper respiratory tract procedures are given to prevent IE caused by viridans streptococci, which are usually highly susceptible to penicillin, while antibiotics for gastrointestinal and urologic procedures are given to prevent IE caused by enterococci which are less susceptible to penicillin. For dental and upper respiratory tract procedures, there

Table 8 Antibiotic prophylaxis for IE—International Consensus

	1 h before the procedure	6 h later
Minimal regimen		
No allergy to penicillin	Amoxycillin 3 g orally	No second dose
Allergy to penicillin	Clindamycin 300–600 mg orally	No second dose
Flexible modifications from minimal to maximal regimen		
Additional doses after the procedure Adjunctive use of aminoglycosides Use of parenteral route of administration		
Maximal regimen		
No allergy to penicillin	Amoxycillin (ampicillin) 2 g IV + gentamicin 1.5 mg/kg IM or IV	1–1.5 g orally
Allergy to penicillin	Vancomycin 1 g in 1-h IV infusion + gentamicin 1.5 mg/kg IM or IV	1 g in 1-h IV infusion[a]

[a] Twelve hours later instead of 6 h later.

are different regimens for patients who can take oral medications, which is the most frequent situation, and for patients under general anesthesia, who require parenteral antibiotics. In all countries, antibiotic regimens are based on penicillins, and alternative regimens have been defined for patients who are allergic to penicillin.

At the present time, comparison of the various national recommendations shows clearly that there are very slight differences from one country to another. It appears that the different regimens from the national guidelines vary within two limits. The minimal and simplest regimen consists of a single oral dose of antibiotic. The maximal regimen relies on multiple doses and the synergistic and prolonged (multiple doses) effect of a cell wall-acting antibiotic and an aminoglycoside, and offers the widest margin of safety (Table 8). The antibiotic regimen for a given patient should be selected between these two limits. It can be proposed that criteria to select the appropriate regimen for a given patient should include the type of cardiac condition at risk, the type, number and duration of the procedure, and the conditions of anesthesia required to perform the procedure (Table 9). This presentation allows the antibiotic prophylaxis to be adapted to each individual situation. It preserves the discretionary nature of the recommendations, the practitioner being responsible for his own patient in a given situation.

CONCLUSIONS

Antibiotic prophylaxis is recommended for cardiac patients at risk who undergo a procedure carrying risk [24]. Present recommendations are close to the maximum that can be done and minimal additional benefits can be obtained by changing these guidelines. Attention has to be concentrated on patients and procedures with the highest risk, i.e. patients with prosthetic valves undergoing dental procedures [25,26]. Major efforts and research are needed to improve the compliance to the recommendations, which are usually made by the experts and used by practitioners and dentists. Diffusion of the information to the appropriate users, and assessment of the knowledge and application of the guidelines by dentists and patients, is required [27].

Since this manuscript was validated by the whole panel, new US recommendations have been published [28] and discussed in the literature [29].

Table 9 Criteria to select the most appropriate antibiotic regimen for prophylaxis of IE—International Consensus

Minimal regimen	Maximal regimen
Cardiac risk	High cardiac risk
Dental procedure	Gastrointestinal or urologic procedure
Single procedure	Multiple procedures
Outpatients	Hospitalized patients
Local anesthesia	General anesthesia

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